Sulfenamide Accelerators
Category Justification and Testing Rationale

CAS Nos.: **102-77-2**; **13752-51-7**
(+ chemicals: 95-31-8; 95-33-0; 4979-32-2 for data purposes)

Rubber and Plastic Additives Panel
American Chemistry Council
November, 2001

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives Panel of the American Chemistry Council include the following member companies: Bayer Corporation, Ciba Specialty Chemicals Corporation, Crompton Corporation, Flexsys America L.P., The Goodyear Tire & Rubber Company, The Lubrizol Corporation, Noveon, Inc., R.T. Vanderbilt Company, Inc., and UOP, LLC.

Executive Summary

The American Chemistry Council's Rubber and Plastic Additives Panel (RAPA), and its member companies, hereby submit for review and public comment their test plan for the Sulfenamide Accelerators category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program.

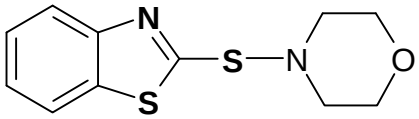
In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted a thorough literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data.

As discussed in the report that follows, the Sulfenamide Accelerators all have the sulfenamide group structure [$=CSNR_2$] attached to a primary or secondary amine and are used as primary accelerators in natural and synthetic rubbers. Their use in rubber products requires negligible water solubility, high organic/oil solubility, relatively low melting point and low vapor pressure. Existing data for members of this category indicate that they are of low to moderate concern for aquatic toxicity, low concern for persistence/bioaccumulation and low concern for mammalian toxicity. They are of moderate concern for skin irritation and allergic skin reaction. We conclude that there is sufficient data on the members of this category and no additional testing is recommended for purposes of the HPV Program.

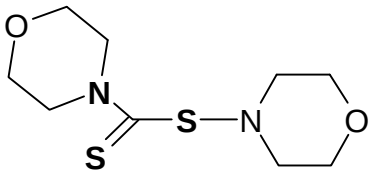
Sulfenamide Accelerators category

As defined by EPA under the HPV Program, a chemical category is "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducing additional testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

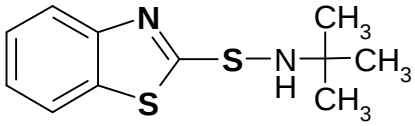
Relying on several factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program,"[1] in which use of chemical categories is encouraged, the following closely related chemicals constitute a chemical category:



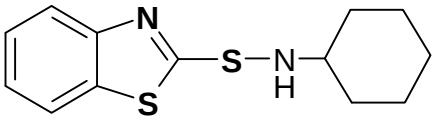
102-77-2
N-oxydiethylenebenzothiazole-2-sulfenamide
(**MBS**)



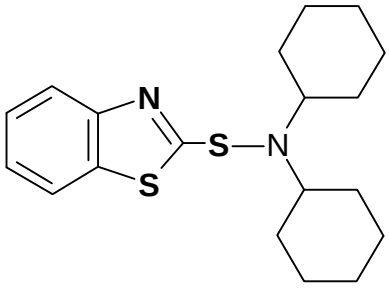
13752-51-7
N-oxydiethylenethiocarbamoyl-N'-oxydiethylenesulfenamide (**OTOS**)



95-31-8
2-benzothiazolesulfenamide, N-tert-butyl
(**TBBS**)



95-33-0
N-cyclohexyl benzothiazole-2-sulfenamide
(**CBS**)



4979-32-2
2-benzothiazolesulfenamide, N,N-dicyclohexyl
(**DCBS**)

Figure 1. Chemical structures

[1] US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. http://www.epa.gov/opptintr/chemrtk/categuid.htm

Structural Similarity

A key factor supporting the classification of these chemicals as a category is their structural similarity. All materials in this category have the sulfenamide group structure [$=CSNR_2$] attached to a primary or secondary amine (in this case, either Morpholine, t-Butylamine, Cyclohexylamine or Dicyclohexylamine).

Activity Similarity

All members of this category function as medium-fast curing primary accelerators in the rubber vulcanization process. They "speed up" the formation of the sulfur crosslinks in natural and synthetic rubbers. There is no other industrial application for the compounds in this category.

Common Precursors

All members of this category are produced via an oxidation reaction using 2-Mercaptobenzothiazole and various primary and secondary amines as starting materials.

Common Breakdown Products

All members of this category readily hydrolize to give the starting amine and, in the case of all but OTOS, 2-Mercaptobenzothiazole. All undergo accelerated degradation when exposed to heat, humidity and/or acidic conditions.

Similarity of Physicochemical Properties

The similarity of the physicochemical properties of these materials parallels their structural similarity. All are room-temperature solids with relatively low melting points, low vapor pressures, negligible water solubility, high flash points, Log P values below 5, and subject to rapid hydrolysis.

Table 1. Physico-chemical Properties

Chemical **CAS#**	2-benzothiazole sulfenamide, N-tert-butyl **95-31-8**	N-Oxydiethylene thiocarbamoly-N'-oxydiethylene sulfenamide **13752-51-7**	N-Oxydiethylene Benzothiazole 2-sulfenamide **102-77-2**	N-cyclohexyl benzothiazole-2-sulphenamide **95-33-0**	2-benzothiazole sulfenamide, N,N-dicyclohexyl **4979-32-2**
Molecular Weight:	238.4	248.36	252.4	264.41	346.6
Melting Point	103 - 109 C	124.3 C (EPI)	75-90 C 150.7ºC (EPI)	93-100 C	96 - 103 C
Boiling Point	No data	353 C (EPI)	decomp 385 C (EPI)	decomp	200 C @1013 hPa decomp
Relative Density	1.29g/cm3 @25 C	0.6 g/cm3	1.35g/cm3 @20 C	1.27g/cm3 @20 C	1.2g/cm3 @20C
Vapour Pressure	1.37 x10(-6)hPa @25 C	1.53x10(-5)hPa	1.34 x10(-6)hPa @25 C	4.0 x10(-7) @25 C	7.5 x10(-4) hPa @120 C
Partition Coefficient (logPow)	4.67	-0.84 (EPI)	3.49 1.025 (EPI)	4.93 3.47 (EPI)	4.8 5.95 (EPI)
Water Solubility	< 1mg/l @ 20 C	62.8 g/l @25 C (EPI)	32ppm 3 gm/l @ 25 C (EPI)	0.24ppm **@**21 C	30mg/l @25 C

= Non-sponsored chemicals; used for data purposes only

EPI = EPIWIN modeling Program. Meylan, W. and Howard, P. (1999), Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

Fate and Transport Characteristic

Members of this category have been shown to rapidly hydrolize to their starting materials, especially under acidic conditions. The presence or absence of light does not significantly alter the degradation rate, so additional photodegradation data collection efforts are not necessary. AOP calculations have been provided for all members of the category. Fugacity Level III calculations have also been provided for all members of the category. In practice, these materials have been shown not to partition to water or air if released into the environment due to their low water solubility and low vapor pressure. Calculated Bioconcentration Factors and Log P values indicate that these materials are not Persistent Organic Pollutants (POPs). For purposes of the HPV Program, additional testing is not necessary for the members of this category. (See Table 2)

Aquatic Toxicology

Data on acute fish toxicity, acute invertebrate toxicity, and algal toxicity were reviewed. The Sulfenamide Accelerators range from moderately toxic to practically non-toxic. Acute studies on *Pimephales* promelas demonstrate a 96-hour LC_{50} ranging from 3.5 mg/l (#102-77-2) to greater than 1000 mg/l (4979-32-2). Acute studies on *Daphnia magna* demonstrate a 48-hour EC_{50} ranging from 4 mg/l (#102-77-2) to greater than 1000 mg/l (4979-32-2). Acute studies on Algae demonstrate a 96-hour EC_{50} ranging from 1.0 mg/l (#95-33-0) to 16 mg/l (4979-32-2). Data are available for most chemicals in this category and ECOSAR modeling data is available for the others; therefore sufficient data is available to adequately evaluate the toxicity to aquatic organisms. For purposes of the HPV Program, no additional aquatic toxicity testing is necessary. (See Table 3)

Mammalian Toxicology – Acute

Data on acute mammalian toxicity were reviewed, and the findings indicate a low concern for acute toxicity for all materials. Data are available for all members of the category by both oral and dermal routes of exposure. Inhalation exposure testing has been done on two members of the category, indicating that the category has been well tested for acute mammalian effects. Therefore, for purposes of the HPV Program, no additional acute mammalian toxicity testing is necessary. (See Table 4)

Mammalian Toxicology – Repeated Dose Toxicity

Data from repeated-dose toxicity studies were reviewed, and sufficient data are available to adequately characterize the repeated dose toxicity of this category. Each member of the category has at least one 28-day, 90-day, or chronic study. For purposes of the HPV Program, additional testing is not necessary for these materials. (See Table 4)

Mammalian Toxicology - Mutagenicity

Data from bacterial reverse mutation assays, *in vitro* and *in vivo* chromosome aberration studies, as well as additional supporting *in vitro* and *in vivo* genetic toxicity studies were reviewed. Data are available for all members of the category. Therefore, the category has been adequately tested for mutagenicity, and for purposes of the HPV Program, no additional mutagenicity testing is necessary. (See Table 4)

Carcinogenicity studies have also been performed on CAS# 102-77-2 (six studies; all negative); 13752-51-7 (compound related effects only at highest dose: 600 ppm); 4979-32-2 (no systemic effects); and 95-33-0 (two studies; both negative).

Mammalian Toxicology - Reproductive and Developmental Toxicity

Data are available for four of five members of the category and indicate a low concern for Reproductive and Developmental Toxicity. These data can be bridged to the other member of the category. Therefore, the category has been adequately tested for Reproductive and Developmental Toxicity and for purposes of the HPV Program, no additional testing is necessary. (See Table 4)

Conclusion

Based upon the data reviewed in the report, the physicochemical and toxicological properties of the proposed Sulfenamide Accelerators category members are similar and follow a regular pattern as a result of that structural similarity. Therefore, the EPA's definition of a chemical category has been met.

Test Plan

The test plan for the Sulfenamide Accelerators category was developed giving careful consideration to the number of animals that would be required for any tests that are not available for certain members of the category and whether these additional tests would provide useful and relevant information. We conclude that there is sufficient data on the members of this category and for purposes of the HPV Challenge Program, no additional testing is recommended. (See Summary Table 5)

Table 2. Matrix of Available and Adequate Data on the Sulfenamide Accelerators Category Environmental Fate

Endpoint	2-benzothiazole sulfenamide, N-tert-butyl **95-31-8**	N-Oxydiethylene thiocarbamoly-N'-oxydiethylene sulfenamide **13752-51-7**	N-Oxydiethylene Benzothiazole 2-sulfenamide **102-77-2**	N-cyclohexyl benzothiazole-2-sulphenamide **95-33-0**	2-benzothiazole sulfenamide, N,N-dicyclohexyl **4979-32-2**
Photodegradation (air)	$T_{1/2}$ = 2.8 hr (AOP)	$T_{1/2}$ = 0.6 hr (AOP)	$T_{1/2}$ = 1.1 hr (AOP) $T_{1/2}$ = 1 hr (water)	$T_{1/2}$ = 1.6 hr (AOP) $T_{1/2}$ = 0.4 hr (water)	$T_{1/2}$ = 1.1 hr (AOP)
Hydrolysis	100% degradation after 25 hr @ pH7	No data	24% degradation afer 25 hr @ pH7	100% degradation after 25 hr @ pH7, 20ºC	Slowly hydrolyzed at 100ºC
Biodegradation	0 % after 28 day (100 mg/l)	No data	0 % after 28 day (100 mg/l)	0 % after 28 day (100 mg/l)	2 % after 28 day (100 mg/l)
Fugacity Level III (EPI)					
Air (%)	0.0114	<0.01	<0.01	<0.01	0.045
Water (%)	23.8	50.2	44.6	20.7	7.15
Soil (%)	76	49.7	55.3	78.3	39.9
Sediment (%)	0.188	0.0927	0.0904	.0924	52.9

= Non-sponsored chemicals used for data purposes only

AOP = AOP Program, version 1.89. EPIWIN modeling Program. Meylan, W. and Howard, P. (1999) Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

EPI = EPIWIN modeling Program. Meylan, W. and Howard, P. (1999) Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

Table 3. Matrix of Available and Adequate Data on the Sulfenamide Accelerators Category Ecotoxicity

Endpoint	2-benzothiazole sulfenamide, N-tert-butyl **95-31-8**	N-Oxydiethylene thiocarbamoly-N'-oxydiethylene sulfenamide **13752-51-7**	N-Oxydiethylene Benzothiazole 2-sulfenamide **102-77-2**	N-cyclohexyl benzothiazole-2-sulphenamide **95-33-0**	2-benzothiazole sulfenamide, N,N-dicyclohexyl **4979-32-2**
Acute Fish Toxicity 96 hr LC50	*L. macrochirus* = > 0.3 mg/l *B. rerio* = 0.5 mg/l *P. promelas* = > 0.3 mg/l *O. mykiss*= > 0.3 mg/l (no toxicity at solubility limit)	Fish = 86 g/l (ECOSAR) Saltwater Fish = 5 g/l (ECOSAR)	*P. promelas* = 3.5 mg/l *L. macrochirus* = 11.5 mg/l *B. rerio* = 1-5 mg/l	*P. promelas* = >1000 mg/l *S. gairdneri* = 5.4 mg/l	*O. latipes* = 1000 mg/l *B. rerio* NOEC =15 mg/l
Acute Invertebrate Toxicity 48 hr EC50	*Daphnia magna* = > 0.3 mg/l (no toxicity at solubility limit)	*Daphnia sp.* = 75 g/l (ECOSAR) Mysidopsis bahia = 188 g/l (ECOSAR)	*Daphnia magna* = 4 – 4.5 mg/l	*Daphnia magna* = 18 mg/l	*Daphnia magna* = >1000 mg/l (24 hrs)
Algal Toxicity 96 hr EC50	*S. capricornutum* = > 0.3 mg/l (no toxicity at solubility limit)	Green algae = 40 g/l (ECOSAR)	Other = 2 mg/l Green algae = 923 mg/l (ECOSAR)	*S. capricornutum* = 0.9-1.1 mg/l	*S. capricornutum* = 16 mg/l (72 hr)

= Non-sponsored chemicals used for data purposes only

ECOSAR = ECOSAR v0.99e. EPIWIN modeling Program. Meylan, W. and Howard, P. (1999) Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

Table 4. Matrix of Available and Adequate Data on the Sulfenamide Accelerators Category Mammalian Toxicity

Endpoint	2-benzothiazole sulfenamide, N-tert-butyl **95-31-8**	N-Oxydiethylene thiocarbamoly-N'-oxydiethylene sulfenamide **13752-51-7**	N-Oxydiethylene Benzothiazole 2-sulfenamide **102-77-2**	N-cyclohexyl benzothiazole-2-sulphenamide **95-33-0**	2-benzothiazole sulfenamide, N,N-dicyclohexyl **4979-32-2**
Acute Toxicity					
Oral LD50	>6310 mg/kg bw (rat)	5,200 mg/kg bw (rat)	12,560 mg/kg bw (rat)	5300 - >8000 mg/kg bw (rat)	1077-10,000 mg/kg bw (rat)
Dermal LD50	6000 – 7940 mg/kg bw (rabbit)	> 10,000 mg/kg bw (rabbit)	>3000 mg/kg bw (rabbit)	> 7940 mg/kg bw (rabbit)	> 2000 mg/kg bw (rabbit)
Inhalation LC50	No data	164.4 mg/l (1 hr) (rat)	> 151 mg/l (1 hr) 0.09 mg/ l (4 hr) (rat)	No data	No data
Repeated Dose NOAEL=	1000 mg/kg bw (28 D – oral, rat) 100 mg/kg bw (90 D –oral- rat) 0.29 mg/l (28 D –inhalation - rat)	200 ppm (2 year – oral, rat)	200 mg/kg bw (28 D – oral, rat) 5 mg/kg bw (113 wk –oral- rat) 9.8 mg/m³ (28 D –inhalation - rat)	250 mg/kg bw (28 D – oral, rat) 014.4 mg/ m³ (28D-inhalation, rat)	<100 mg/kg bw (44 D – oral, rat)
Mutagenicity – gene mutation	Ames = negative *E. coli* = negative HGPRT = negative CHO gene mutation = negative MLA = positive	Ames = negative *E. coli* = negative MLA = positive	Ames = negative CHO gene mutation = negative MLA = positive (+act)	Ames = negative yeast gene mutation = negative MLA = negative	Ames = negative *E. coli* = negative HGPRT = negative
Mutagenicity – chromosome aberration	*E. coli* DNA Damage & Repair = ambiguous	CHO cytogenic assay = positive (-act) *E. coli* DNA Damage & Repair = positive *In vivo* Dom. Lethal = negative	SCE = negative CHO cytogenic assay = negative *E. coli* DNA Damage & Repair = negative Dom. Lethal = negative	No data	*In* vivo (rat) cytogenic assay = negative UDS = negative
Reproductive Toxicity	No data	No effects on reproduction at doses up to 600 ppm (rat)	No effects on reproduction at doses up to 500 mg/kg bw (rat)	No effects on reproduction at doses up to: 0.5% (rat) 2000 mg/kg bw (rat)	No effects on reproduction at doses up to 400 mg/kg bw (rat)
Developmental Toxicity NOAEL =	>500 mg/kg bw (rat)	No data	1000 mg/kg bw (rat)	500 mg/kg bw (rat)	<400 mg/kg bw (rat)

Legend for Table 4:

(+act) = with metabolic activation
(-act) = without metabolic activation
CHO = Chinese hamster ovary cells
MLA = mouse lymphona assay
SCE = Sister chromatid exchange
UDS = Unscheduled DNA Synthesis

= Non-sponsored chemicals used for data purposes only.

Table 5. Test Plan for the Sulfenamide Accelerator Category

Test	2-benzothiazole sulfenamide, N-tert-butyl **95-31-8**	N-Oxydiethylene thiocarbamoly-N'-oxydiethylene sulfenamide **13752-51-7**	N-Oxydiethylene Benzothiazole 2-sulfenamide **102-77-2**	N-cyclohexyl benzothiazole-2-sulphenamide **95-33-0**	2-benzothiazole sulfenamide, N,N-dicyclohexyl **4979-32-2**
Environmental Fate					
Photodegradation	C	C	A,C	A,C	C
Hydrolysis	A	R	A	A	A
Biodegradability	A	R	A	A	A
Fugacity Level III	C	C	C	C	C
Ecotoxicology					
Acute Fish Toxicity	A	C,R	A	A	A
Acute Invertebrate Toxicity	A	C,R	A	A	A
AlgaL Toxicity	A	C,R	A,C	A	A
Mammalian Toxicology					
Acute Toxicity	A	A	A	A	A
Repeated Dose	A	A	A	A	A
Mutagenicity – gene mutation	A	A	A	A	A
Mutagenicity – chromosome	A	A	A	NR	A
Reproductive Toxicity	NR	A	A	A	A
Developmental Toxicity	A	R	A	A	A

= Non-sponsored chemicals used for data purposes only.

Legend for Table 5:
A = Adequate data available
R = Endpoint requirement fulfilled using category approach, SAR
C = Endpoint requirement fulfilled based on calculated data
T = Testing to be done
NR = No testing required; chemical not sponsored

Background Information: Manufacturing and Commercial Applications

Manufacturing

The Sulfenamide Accelerator class of rubber accelerators have been manufactured in the USA for over 60 years. While there have been some modest process improvements to yield and quality, the general batch manufacturing process involves the controlled oxidation of, typically, 2-Mercaptobenzothiazole, and one of several primary amines as starting materials. The reaction is carried out using water as a solvent.

Commercial Applications

The sole commercial use of the Sulfenamide Accelerator compounds is as general purpose cure rate accelerators for natural and synthetic rubber vulcanization. They are widely used in the manufacture of automotive components and industrial rubber products such as tires, hoses, conveyer belts, bushings, seals, gaskets and windshield wiper blades. Shoe soles, rubber bands and racquet balls also use this class of compounds, as they are economical, easy to use, and allow comfortable processing safety margins for cure rate control. Typical usage for Sulfenamide accelerators is from 0.5 to 4 parts accelerator per every 100 parts of rubber (phr).

Shipping/Distribution

Sulfenamide Accelerator materials are shipped extensively throughout the world from manufacturing plants located in North America, South America, Europe, Asia and Africa.

Worker/Consumer Exposure

Compounds in this category are sold only to large industrial users as ingredients for their rubber compounding processes. There are no other uses for these compounds, nor any direct consumer applications, and therefore no direct sales to the general public.

The following chemicals have been "Regulated for Use" by the Food and Drug Administration for various food-contact applications in the following sections of 21 CFR:

177.2600	Rubber Articles	CBS, MBS, TBBS

The rubber and plastics additives industry has a long safety record and only sophisticated industrial users handle these materials. Exposure of workers handling Sulfenamide accelerator materials is likely to be the highest in the area of material packaging rather than from chemical manufacturing. These materials are made as pellets, powders and flakes. Product forms that minimize dust generation, coupled with the mechanized materials handling systems of the large industrial users, combine to keep exposures to minimum levels. However, during material packout at the manufacturing site and, to a somewhat lesser degree during weigh-up activities at the customer site, there is a potential for skin and inhalation exposure (nuisance dust is the primary route of worker exposure).

Consumer exposure is minimal. Only very small amounts are used in rubber processing, and the materials themselves become bound in the rubber matrix during the vulcanization process. The most likely route of consumer exposure is skin contact from rubber or latex articles. Skin irritation, or possibly an allergic skin reaction may occur, but only in sensitive individuals subjected to prolonged and repeated exposure, especially under moist conditions.